UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

October 27, 2008

MEMORANDUM

Subject:	Name of Pesticide Product:	XEDAMATE A
	EPA Reg. No. /File Symbol:	64864-AE
	DP Barcode:	DP 354300
	Decision No.:	393722
	Action Code:	R310
	PC Codes:	018301 (Chlorpropham) 820700 (Oils, clove)

From: Byron T. Backus, Ph.D., Toxicologist
Technical Review Branch
Registration Division (7505P)

To: Rosemary Kearns/Tony Kish, RM 22
Fungicide Branch
Registration Division (7505P)

Registrant: PACE INTERNATIONAL LLC

FORMULATION FROM LABEL:

Active Ingredient(s):	% by wt.
018301 Chlorpropham*	55.4%
820700 Oils, clove	43.5%
Other Ingredient(s):	1.1%
TOTAL	100.0%

*Contains 5.3 lbs chlorpropham per gallon

ACTION REQUESTED: The Risk Manager requests:

"TRB-acute tox – Registrant has submitted the following documents in support of the new registration of Xedamate A, an end-use product containing 55.4% chlorpropham and 43.5% clove oil for post-harvest use on potatoes to control sprouting: 47425508 acute oral toxicity in rats acute toxic class method; 47425509 acute dermal toxicity in rats; 47425510 acute inhalation (nose only) study in the rat; 47425511 acute irritant/corrosive effect on the eyes; 47425512 acute

irritant/corrosive effect on the skin; 47425513 assessment of sensitising properties on albino guinea pigs maximisation test accord to Magnusson and Kligman; and proposed labelling, CSF, data matrix and certification with respect to citation of data form…"

BACKGROUND:

The material received for review includes (MRIDs 47425508 through 47425513) a 6-pack of acute toxicity studies.

In addition this package includes a copy of the label (with declarations of 55.4% Chlorpropham and 43.5% Clove oil as the two actives) and a CSF dated May 6, 2008.

COMMENTS AND RECOMMENDATIONS:

1. An Agency contractor, Oak Ridge National Laboratory, conducted the primary review of the 6 acute toxicity studies. TRB performed the secondary review and made changes as necessary.

2. The 6 acute toxicity studies have all been classified as acceptable. These studies adequately satisfy the acute toxicity study requirements to support the registration of this proposed product.

3. The following is the acute toxicity profile for EPA File Symbol 64864-AE, based on the results of the acute toxicity studies:

Acute oral toxicity	III	Acceptable	MRID 47425508
Acute dermal toxicity	III	Acceptable	MRID 47425509
Acute inhalation toxicity	IV	Acceptable	MRID 47425510
Primary eye irritation	III	Acceptable	MRID 47425511
Primary dermal irritation	III	Acceptable	MRID 47425512
Dermal sensitization	Sensitizer	Acceptable	MRID 47425513

4. Based on the acute toxicity profile above, the following would be the precautionary and first aid labeling, as obtained from the Label Review System:

PRODUCT ID #: **064864-00062**

PRODUCT NAME: **XEDAMATE A**

PRECAUTIONARY STATEMENTS

SIGNAL WORD: **CAUTION**

Hazards to Humans and Domestic Animals:

Harmful if absorbed through skin. Harmful if swallowed. Causes moderate eye irritation. Avoid contact with skin, eyes or clothing. Wash thoroughly with soap and water after handling and before eating, drinking, chewing gum, or using tobacco. Wear long-sleeved shirt and long pants, socks, shoes, and chemical-resistant gloves (such as Natural Rubber, Selection Category A). Remove and wash contaminated clothing before reuse. [Wear protective eyewear.]*

Prolonged or frequently repeated skin contact may cause allergic reactions in some individuals.

*[Protective eyewear may be specified, if appropriate].

First Aid:

If on skin:
-Take off contaminated clothing.
-Rinse skin immediately with plenty of water for 15-20 minutes.
-Call a poison control center or doctor for treatment advice.

If swallowed:
-Call a poison control center or doctor immediately for treatment advice.
-Have person sip a glass of water if able to swallow.
-Do not induce vomiting unless told to by a poison control center or doctor.
-Do not give anything to an unconscious person.

If in eyes:
-Hold eye open and rinse slowly and gently with water for 15-20 minutes.
-Remove contact lenses, if present, after the first 5 minutes, then continue rinsing.
-Call a poison control center or doctor for treatment advice.

NOTE TO PHYSICIAN: Note to PM/CRM/Registrant: The proposed label should contain a "Note to Physician". The following statements are suggested types of information that may be included, if applicable: - technical information on symptomatology; - use of supportive treatments to maintain life functions; - medicine that will counteract the specific physiological effects of the pesticide; - company telephone number to specific medical personnel who can provide specialized medical advice.

Have the product container or label with you when calling a poison control center or doctor or going for treatment. You may also contact 1-800-xxx-xxxx for emergency medical treatment information.

5. The CSF (dated May 6, 2008) for 64864-AE should also be reviewed and accepted by the TRB Chemistry Team.

DATA EVALUATION RECORD

OILS, CLOVE - CHLORPROPHAM

STUDY TYPE: ACUTE ORAL TOXICITY - RAT [OPPTS 870.1100; OECD 423]
ACUTE DERMAL TOXICITY - RAT [OPPTS 870.1200; OECD 402]
ACUTE INHALATION TOXICITY - RAT [OPPTS 870.1300; OECD 403]
ACUTE EYE IRRITATION - RABBIT [OPPTS 870.2400; OECD 405]
ACUTE DERMAL IRRITATION - RABBIT [OPPTS 870.2500; OECD 404]
DERMAL SENSITIZATION - GUINEA PIG [OPPTS 870.2600; OECD 406]
MRID: 47425508, 47425509, 47425510, 47425511, 47425512 and 47425513

Prepared for

Registration Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
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2777 South Crystal Drive
Arlington, VA 22202

Prepared by

Toxicology and Hazard Assessment Group
Environmental Sciences Division
Oak Ridge National Laboratory
Oak Ridge, TN 37831
Task Order No. 1-29

Primary Reviewer:
Donna L. Fefee, D.V.M. Signature: _____
Date: _____

Secondary Reviewers:
Dana F. Glass, D.V.M. Signature: _____
Date: _____

Robert H. Ross, M.S., Group Leader Signature: _____
Date: _____

Quality Assurance:
Kimberly G. Slusher, M.S. Signature: _____
Date: _____

Disclaimer

This review may have been altered subsequent to the contractor's signatures above.

Oak Ridge National Laboratory managed and operated by UT-Battelle, LLC., for the U.S. Department of Energy under Contract No. DE-AC05-00OR22725.

Reviewer: Byron T. Backus, Ph.D. **Date:** October 23, 2008
Risk Manager (EPA): 22

STUDY TYPE: Acute Oral Toxicity – Rat; OPPTS 870.1100; OECD 423

TEST MATERIAL: Xedamate-60; Batch No. XL 2011; brown liquid; stored at room temperature. From information received on 10/20/2008 from Lewis & Harrison LLC the material tested contained 58.48 ± 0.77% Chlorpropham and 41.52 ± 0.77% Clove Oil.

CITATION: Richeux, F. (2002) Xedamate-60: assessment of acute oral toxicity in rats - acute toxic class method. Study Number TAO423-PH-02/0132. Unpublished study prepared by Phycher Bio développement, Cestas, France. October 3, 2002. MRID 47425508.

SPONSOR: Xeda International, Saint Andiol, France. [Submitter is Pace International LLC, Seattle, Washington.]

EXECUTIVE SUMMARY: In an acute oral toxicity study (MRID 47425508), two groups of three male and three female Sprague-Dawley (SPF Caw) rats were given single oral gavage doses of undiluted Xedamate-60 (Batch No. XL 2011; 58.48% ± 0.77% Chlorpropham and 41.52 ± 0.77% Clove oil) or distilled water, both at doses of 2000 mg/kg bw (the dosage volume of Xedamate-60 was 1786 mL/kg, indicating a specific gravity of 1.12 (according to the information received 10/20/2008 the specific gravity was 1.128). Dosing was on day 0, and the animals were subsequently observed for 14 days. The animals were supplied by IFFA CREDO, L'Arbresle, France (males: 184-198 g; females: 162-175 g); the ages of the animals were not reported.

There were no deaths. One hour after dosing, all treated males and two treated females exhibited decreased spontaneous activity, decreased muscle tone, and partly closed eyes, and both affected females also had slowed respiration with one having an absent noise (Preyer's) response. All animals fully recovered within 24 hours of treatment, and gained weight throughout the study; however, decreased body weight gain over days 0-2 was seen in both males and females (-55% and -36%, respectively) relative to their controls. There were no abnormal gross necropsy findings.

LD_{50} Males > 2000 mg/kg bw
LD_{50} Females > 2000 mg/kg bw
LD_{50} Combined > 2000 mg/kg bw

Based on the acute oral LD_{50}, Xedamate-60 is in EPA Toxicity Category III for oral toxicity.

This study is classified as acceptable. It does satisfy the guideline requirements for an acute oral study (OPPTS 870.1100; OECD 423) in the rat.

COMPLIANCE: Signed and dated GLP, Quality Assurance and Data Confidentiality statements were provided.

RESULTS and DISCUSSION:

Animals were dosed as follows:

Animal Number	Sex	Dose Level (mg/kg)	Long-Term Outcome
Rm 2033	Male	0[a]	S
Rm 2034	Male	0[a]	S
Rm 2035	Male	0[a]	S
Rf 2024	Female	0[a]	S
Rf 2025	Female	0[a]	S
Rf 2026	Female	0[a]	S
Rm 2039	Male	2000	S
Rm 2040	Male	2000	S
Rm 2041	Male	2000	S
Rf 2030	Female	2000	S
Rf 2031	Female	2000	S
Rf 2032	Female	2000	S

S = Survival, D = Death
[a]Dosed with distilled water at 2000 mg/kg.

A. Mortality: There were no deaths.

B. Clinical observations: One hour after dosing, all treated males and two treated females exhibited decreased spontaneous activity, decreased muscle tone, and partly closed eyes, and both affected females also had slowed respiration with one having an absent noise (Preyer's) response. All animals fully recovered within 24 hours of treatment, and gained weight throughout the study; however decreased body weight gain over days 0-2 was seen in both males and females (-55% and -36%, respectively) relative to their controls.

C. Gross necropsy: There were no abnormal findings.

D. Reviewer's conclusions: In agreement with the study author, the acute oral LD_{50} for males, females, and the combined sexes is greater than 2000 mg/kg bw. This places the test material in EPA Toxicity Category III for oral toxicity.

E. Reviewer's note: As study deficiencies, the test material characterization did not include the percentage(s) of the active ingredient(s) [this was obtained by the EPA reviewer on 10/20/2008], and the ages of the animals were not reported.

STUDY TYPE: Acute Dermal Toxicity – Rat; OPPTS 870.1200; OECD 402

TEST MATERIAL: Xedamate-60; Batch No. XL 2011; brown liquid; stored at room temperature. From information received on 10/20/2008 from Lewis & Harrison LLC the material tested contained 58.48 ± 0.77% Chlorpropham and 41.52 ± 0.77% Clove Oil.

CITATION: Richeux, F. (2002) Xedamate-60: assessment of acute dermal toxicity in rats. Study Number TAD-PH-02/0132. Unpublished study prepared by Phycher Bio développement, Cestas, France. October 3, 2002. MRID 47425509.

SPONSOR: Xeda International, Saint Andiol, France. [Submitter is Pace International LLC, Seattle, Washington.]

EXECUTIVE SUMMARY: In an acute dermal toxicity study (MRID 47425509), two groups of five male and five female Sprague-Dawley (SPF Caw) rats were dermally exposed for 24 hours to undiluted Xedamate-60 (Batch No. XL 2011; 58.48% ± 0.77% Chlorpropham and 41.52 ± 0.77% Clove oil) or distilled water at doses of 2000 mg/kg bw. The doses were applied to intact skin and covered with a porous gauze dressing. The animals were then observed for 14 days, including observation of the dose sites for dermal irritation. The animals were supplied by IFFA CREDO, L'Arbresle, France (males: 199-216 g; females: 173-196 g); the ages of the animals were not reported.

There were no deaths, abnormal clinical signs, or abnormal gross necropsy findings. Two control females and two treated females lost weight over days 0-2, and a different treated female lost weight over days 2-7, but all of these animals gained sufficient weight during the other intervals so that final body weights exceeded initial. The rest of the animals gained weight throughout the study.

LD_{50} Males > 2000 mg/kg bw
LD_{50} Females > 2000 mg/kg bw
LD_{50} Combined > 2000 mg/kg bw

Based on the acute dermal LD_{50}, the test material is in EPA Toxicity Category III for dermal toxicity.

This study is classified as acceptable. It does satisfy the guideline requirements for an acute dermal study (OPPTS 870.1200; OECD 402) in the rat. It should be noted that the semi-occlusive (or occlusive) coverings specified in OPPTS 870.1200 were not used.

COMPLIANCE: Signed and dated GLP, Quality Assurance and Data Confidentiality statements were provided.

RESULTS and DISCUSSION:

Dose (mg/kg bw)	Mortality/Number tested		
	Males	Females	Combined
0	0/5	0/5	0/10
2000	0/5	0/5	0/10

A. Mortality: There were no deaths

B. Clinical observations: No abnormal clinical signs, including irritation at the application site, were reported. Two control females and two treated females lost weight over days 0-2, and a different treated female lost weight over days 2-7, but all of these animals gained sufficient weight during the other intervals so that final body weight exceeded initial. The rest of the animals gained weight throughout the study.

C. Gross necropsy: There were no abnormal findings.

D. Reviewer's conclusions: Under the conditions used in this study, the acute dermal LD_{50} for males, females, and the combined sexes is greater than 2000 mg/kg bw, and this places the test material in EPA Toxicity Category III. From the available information, it appears that the semi-occlusive (or occlusive) coverings specified in OPPTS 870.1200 were not used, but these are not mentioned in OECD 402.

E. Reviewer's note: As study deficiencies, the test material characterization did not include the percentage(s) of the active ingredient(s) [this was obtained by the EPA reviewer on 10/20/2008], and the ages of the animals were not reported. The study author did not fully describe the methods used, including when and the manner in which the application site was prepared or the size or location of the application site. The study author cited a study protocol and stated that it was in accordance with OECD 402, but a copy of the protocol was not provided.

Reviewer: Byron T. Backus, Ph.D. **Date:** October 27, 2008
Risk Manager (EPA): 22

STUDY TYPE: Acute Inhalation Toxicity – Rat; OPPTS 870.1300; OECD 403

TEST MATERIAL: Xedamate-60; Batch No. XL 2011; yellow-brown slightly viscous liquid; stored at room temperature in the dark. From information received on 10/20/2008 from Lewis & Harrison LLC the material tested contained 58.48 ± 0.77% Chlorpropham and 41.52 ± 0.77% Clove Oil. On p. 10 of MRID 47425510 it is stated that the purity was 97.5%; according to information received by this reviewer on October 27, 2008 it refers to the minimum purity of the formulation.

CITATION: Wesson, C. (2002) Xedamate-60: acute inhalation toxicity (nose only) study in the rat. Study Number 1620/041. Unpublished study prepared by Safepharm Laboratories Limited, Derby, United Kingdom. November 18, 2002. MRID 47425510.

SPONSOR: Xeda International, Saint Andiol, France. [Submitter is Pace International LLC, Seattle, Washington.]

EXECUTIVE SUMMARY: In an acute inhalation toxicity study (MRID 47425510), five male and five female Sprague-Dawley CD® (SD) IGS BR rats were exposed for 4 hours by nose-only inhalation to undiluted Xedamate-60 (97.5% a.i.; Batch No. XL 2011; according to information received 10/20/2008 from Lewis & Harrison LLC the material tested contained 58.48% ± 0.77% Chlorpropham and 41.52% ± 0.77% Clove Oil) as an aerosol with a mean gravimetric concentration of 4.67 mg/L, MMAD of 2.35, GSD of 2.09, and inhalable fraction of 76.4%. Exposure was on day 0, and the animals were observed for 14 days. The animals were 8-12 weeks old (males: 300-336 g; females: 218-236 g) and supplied by Charles River (UK) Ltd, Margate, Kent.

There were no deaths or abnormal gross necropsy findings, and all of the animals gained weight during both weeks of the study. During exposure, four males and all females had increased or decreased respiratory rate, and one female had labored respiration. Upon removal from the tube and one hour later, all of the animals had increased respiratory rate, noisy respiration, hunched posture, and piloerection, while one male had labored respiration. Other abnormalities during and after exposure on day 0 included wet fur and red or brown staining around the eyes and/or snout. All of the animals recovered by day 7 and remained normal for the remainder of the study.

LC_{50} Males > 4.67 mg/L
LC_{50} Females > 4.67 mg/L
LC_{50} Combined > 4.67 mg/L

Based on the four-hour inhalation exposure LC_{50}, the test material is in EPA Toxicity Category IV by the inhalation exposure route.

This study is classified as acceptable. It does satisfy the guideline requirements for an acute inhalation study (OPPTS 870.1300; OECD 403) in the rat.

COMPLIANCE: Signed and dated GLP, Quality Assurance and Data Confidentiality statements were provided.

RESULTS and DISCUSSION:

Nominal Conc. (mg/L)	Gravimetric Conc. (mg/L)	MMAD (μm)	GSD	Mortality/Number Tested		
				Males	Females	Combined
23.24	3.24-7.58	2.35	2.09	0/5	0/5	0/10

Test atmosphere / Chamber description: The exposure atmosphere was generated by using an infusion pump to deliver the test material to a glass concentric jet nebulizer supplied with filtered compressed air. The nebulizer was located at the top of the cylindrical nose-only exposure chamber, which had an internal volume of approximately 30 L.

Gravimetric Conc. (mg/L):	3.24-7.58
Chamber Volume (L):	Approximately 30
Total Airflow (L/min):	30
Temperature (° C):	18-21
Relative Humidity (%):	68-69
Time to equilibrium (minutes):	5 minutes

Test atmosphere concentration: Prior to the start of the study, the mean non-volatile component of the test material was found to be 88.54%. Samples were collected from the breathing zone of the animals at 17 intervals during exposure by using a vacuum pump to draw 2 Liters of the test atmosphere through a pre-weighed glass fiber filter. The filters were dried and reweighed, and the weight difference was divided by the volume of air sampled to determine the chamber concentration in terms of the non-volatile component of the test material. This value and the mean non-volatile component were then used to attain the concentration of the test material itself.

Particle size determination: Three samples were withdrawn from the breathing zone of the animals by using a vacuum pump to draw a known volume of atmosphere through a six-stage Marple Personal Cascade Impactor. The mean weight of the test material collected at each stage was determined, and the mass median aerodynamic diameter (MMAD), geometric standard deviation (GSD), and the percentage of the aerosol that was less than 4μm (the respirable fraction) were determined using computer software (Chrom Series Data Server and Reg 2000 Graph Plotter).

A. Mortality: There were no deaths.

B. Clinical observations: During exposure, four males and all females had increased or decreased respiratory rate, and one female had labored respiration. Upon removal from the tube and one hour later, all of the animals had increased respiratory rate, noisy respiration,

hunched posture, and piloerection, while one male had labored respiration. Other abnormalities during and after exposure on day 0 included wet fur and red or brown staining around the eyes and/or snout. All of the animals recovered by day 7 and remained normal for the remainder of the study. All of the animals gained weight during both weeks of the study.

C. Gross necropsy: There were no abnormal findings.

D. Reviewer's conclusions: In agreement with the study author the four-hour inhalation exposure LC_{50} for males, females, and the combined sexes is greater than 4.67 mg/L. This places the test material in EPA Toxicity Category IV by the inhalation exposure route.

E. Primary Reviewer's note: Three samples were collected for particle size determination, but rather than determining separate MMAD and GSD values for each sample, the mean weight of the test material collected at each stage was determined, and the data were used to determine single "mean" MMAD and GSD values. Evaluating the data in this manner does not demonstrate whether the MMAD was consistent over time, and this is a serious deficiency. Comment by EPA Reviewer: The graph presented in Figure 3 (p. 22 of MRID 47425510) shows a consistency in particle size distribution for the 3 collected samples.

Reviewer: Byron T. Backus **Date:** October 23, 2008
Risk Manager (EPA): 22

STUDY TYPE: Primary Eye Irritation – Rabbit; OPPTS 870.2400; OECD 405

TEST MATERIAL: Xedamate-60; Batch No. XL 2011; brown liquid; stored at room temperature. From information received from Lewis & Harrison LLC on 10/20/2008 the material tested contained 58.48 ± 0.77% Chlorpropham and 41.52 ± 0.77% Clove Oil.

CITATION: Richeux, F. (2002) Xedamate-60: assessment of acute irritant/corrosive effect on the eyes. Study Number IO-OCDE-PH-02/0132. Unpublished study prepared by Phycher Bio développement, Cestas, France. October 3, 2002. MRID 47425511.

SPONSOR: Xeda International, Saint Andiol, France. [Submitter is Pace International LLC, Seattle, Washington.]

EXECUTIVE SUMMARY: In a primary eye irritation study (MRID 47425511), 0.1 mL of undiluted Xedamate-60 (Batch No. XL 2011; 58.48% ± 0.77% Chlorpropham and 41.52 ± 0.77% Clove oil) was instilled into the conjunctival sac of the one eye of three male New Zealand rabbits. Instillation was on day 1, and eyes were scored for ocular irritation 1, 24, 48, and 72 hours after instillation, and then daily up to day 9. The untreated contralateral eye of each animal served as a control. The animals weighed 2.19-2.57 kg and were supplied by the Elevage de Gérome (Quartier Labaste, Linxe, France); the ages of the animals were not reported.

One hour after instillation, grade 1 conjunctival redness and discharge and grade 2 chemosis were seen in all treated eyes. At 24 hours, grade 2 conjunctival redness, chemosis, and discharge were seen in three eyes, grade 1 iritis was seen in two eyes, and grade 2 corneal opacity was seen in three eyes. The conjunctivitis resolved by day 8 or 9 (i.e. 7 or 8 days post-instillation), with one eye being still positive (score of 2 or greater) on Day 6 (i.e. 5 days post-instillation); subsequent scores for conjunctival irritation were zero or 1 (not considered positive). The iritis resolved in one eye prior to the 48 hour observation and resolved in the other eye prior to day 6 (i.e. 5 days post-instillation). The corneal opacity resolved prior to day 5, 6, or 8 (i.e. 4, 5, or 7 days post-instillation) in the three different animals. Additional observations included purulent secretion in one eye on days 2 and 3 and corneal neovascularization in two eyes on days 4 and 5. As all corneal opacity scores were zero on day 8 (which was 7 days after eyes were treated with the test material), and as the maximum scores for conjunctival irritation on the day were 1, the eyes were not positive for irritation 7 days after instillation.

In this study, there was eye irritation from 1 hour (all 3 eyes) to 6 days (one eye) after instillation, but none of the eyes was positive for irritation on day 7. Xedamate-60 is classified as EPA Toxicity Category III for primary eye irritation.

This study is classified as acceptable. It does satisfy the guideline requirements for a primary eye irritation study (OPPTS 870.2400; OECD 405) in the rabbit.

COMPLIANCE: Signed and dated GLP, Quality Assurance and Data Confidentiality statements were provided.

RESULTS and DISCUSSION:

Observations	Number "positive"/Number treated						
	Hours				Days[a]		
	1	24	48	72	5	7	8
Corneal Opacity	0/3	3/3	3/3	3/3	1/3	0/3	0/3
Iritis	0/3	2/3	1/3	1/3	0/3	0/3	0/3
Conjunctivae:							
Redness*	0/3	3/3	1/3	1/3	1/3	0/3	0/3
Chemosis*	3/3	3/3	1/3	1/3	0/3	0/3	0/3
Discharge**	0/3	3/3	1/3	1/3	1/3	0/3	0/3

[a] Days after instillation; Day 5 in this table is Day 6 of Table 5 in MRID 47425511 (instillation was on Day 1)
* Score of 2 or more required to be considered "positive"
** Discharge does not indicate a positive effect according to the grading scale

A. Observations: One hour after instillation of the test material, the three treated eyes had grade 1 conjunctival redness and discharge and grade 2 chemosis. At 24 hours, grade 2 conjunctival redness, chemosis, and discharge were seen in three eyes, grade 1 iritis was seen in two eyes, and grade 2 corneal opacity was seen in three eyes. The iritis resolved in one eye prior to the 48 hour observation and resolved in the other eye prior to day 6 (i.e. 5 days post-instillation). The corneal opacity resolved prior to day 5, 6, or 8 (i.e. 4, 5, or 7 days post-instillation) in the three different animals. The conjunctivitis resolved by day 8 or 9 (i.e. 7 or 8 days post-instillation). Additional observations included purulent secretion in one eye on days 2 and 3 and corneal neovascularization in two eyes on days 4 and 5.

B. Results: The maximum mean total score was 42.0, recorded at 24 hours after instillation of the test material.

C. Reviewer's conclusions: The test material caused eye irritation effects which had cleared by day 7, and is classified as EPA Toxicity Category III.

D. Reviewer's note: As a deficiency, the test material characterization in the original report did not include the percentage(s) of the active ingredient(s).

Reviewer: Byron T. Backus, Ph.D. **Date:** October 27, 2008
Risk Manager (EPA): 22

STUDY TYPE: Primary Dermal Irritation – Rabbit; OPPTS 870.2500; OECD 404

TEST MATERIAL: Xedamate-60; Batch No. XL 2011; brown liquid; stored at room temperature. From information received from Lewis & Harrison LLC on 10/20/2008 the material tested contained 58.48 ± 0.77% Chlorpropham and 41.52 ± 0.77% Clove Oil.

CITATION: Richeux, F. (2002) Xedamate-60: assessment of acute irritant/corrosive effect on the skin. Study Number IC-OCDE-PH-02/0132. Unpublished study prepared by Phycher Bio développement, Cestas, France. October 3, 2002. MRID 47425512.

SPONSOR: Xeda International, Saint Andiol, France. [Submitter is Pace International LLC, Seattle, Washington.]

EXECUTIVE SUMMARY: In a primary dermal irritation study (MRID 47425512), three female New Zealand albino rabbits were dermally exposed to 0.5 mL of undiluted Xedamate-60 (Batch No. XL 2011; 58.48% ± 0.77% Chlorpropham and 41.52 ± 0.77% Clove oil) for 4 hours "under semi-occlusive dressing." The doses were applied to undamaged skin on the right flank, and a 0.5 mL volume of distilled water was applied to the left flank as a control. The animals were observed at 1, 24, 48, and 72 hours and up to 9 days after patch removal, and irritation at the dose sites was scored according to Draize. The animals weighed 2.27-2.50 kg ("during the test") and were supplied by the Elevage de Gérome (Quartier Labaste, Linxe, France); the ages of the animals were not reported.

At one hour, grade 1 erythema was seen on all three treated application sites. At 24 hours, grade 2 erythema was seen on three sites and grade 1 edema was present on two. On the application site without edema, the erythema improved to grade 1 at 48 hours and resolved by day 5 (i.e. 4 days after application). The erythema on the other two sites was grade 2 (for both) at 48 hours, grade 1-2 at 72 hours, grade 1 (for both) on days 5-6 (4-5 days post-application), and resolved on day 7, while the edema on these sites remained at grade 1 through 72 hours, then resolved. Additional observations on the latter two sites included dryness on days 5-7; these two sites were normal on day 8 (i.e. 7 days post application).

In this study, the formulation is a moderate irritant. Xedamate-60 is classified as EPA Toxicity Category III for primary dermal irritation. The Primary Irritation Index (PII) = 2.00, and the mean score at 72 hours was 2.00.

This study is classified as acceptable. It does satisfy the guideline requirements for a primary dermal irritation study (OPPTS 870.2500; OECD 404) in the rabbit.

COMPLIANCE: Signed and dated GLP, Quality Assurance and Data Confidentiality statements were provided.

RESULTS and DISCUSSION:

Animal Number	Sex	Hours			
		1	**24**	**48**	**72**
A4659	Female	1/0 [a]	2/0	1/0	1/0
A4657	Female	1/0	2/1	2/1	2/1
A4658	Female	1/0	2/1	2/1	1/1
Severity of Irritation: Mean Score		1.00/0.00	2.00/0.67	1.67/0.67	1.33/0.67

[a] Erythema/Edema

A. Observations: At one hour, grade 1 erythema was seen on all three treated application sites. At 24 hours, grade 2 erythema was seen on three sites and grade 1 edema was present on two. On the application site without edema, the erythema improved to grade 1 at 48 hours and resolved by day 5 (i.e. 4 days after application). The erythema on the other two sites was grade 2 (for both) at 48 hours, grade 1-2 at 72 hours, grade 1 (for both) on days 5-6 (4-5 days post-application), and resolved on day 7, while the edema on these sites remained at grade 1 through 72 hours, then resolved. Additional observations on the latter two sites included dryness on days 5-7; these two sites were normal on day 8 (i.e. 7 days post application).

B. Results: The primary irritation index (PII) was 2.00. The mean irritation score at 72 hours was 2.00.

C. Reviewer's conclusions: Under the conditions used in this study, the test material is a moderate irritant and is classified as EPA Toxicity Category III.

D. Reviewer's note: As a deficiency, the test material characterization did not include the percentage(s) of the active ingredient(s). The study author did not fully describe the methods used, including when and the manner in which the application site was prepared, the size of the application site, or the manner in which the application site was covered post-application. The study author cited a study protocol and stated that it was in accordance with OECD 404, but a copy of the protocol was not provided.

Reviewer: Byron T. Backus, Ph.D. **Date:** October 27, 2008
Risk Manager (EPA): 22

STUDY TYPE: Dermal Sensitization –Guinea Pig; OPPTS 870.2600; OECD 406

TEST MATERIAL: Xedamate-60; Batch No. XL 2011; brown liquid; stored at room temperature. From information received from Lewis & Harrison LLC on 10/20/2008 the material tested contained 58.48 ± 0.77% Chlorpropham and 41.52 ± 0.77% Clove Oil.

CITATION: Richeux, F. (2002) Xedamate-60: assessment of sensitising properties on albino guinea pig maximisation test according to Magnusson and Kligman. Study Number SMK-PH-02/0132. Unpublished study prepared by Phycher Bio développement, Cestas, France. October 3, 2002. MRID 47425513.

SPONSOR: Xeda International, Saint Andiol, France. [Submitter is Pace International LLC, Seattle, Washington.]

EXECUTIVE SUMMARY: In a dermal sensitization study (MRID 47425513) with Xedamate-60 (Batch No. XL 2011; 58.48% ± 0.77% Chlorpropham and 41.52 ± 0.77% Clove oil) in physiological saline, 21 female Dunkin Hartley albino guinea pigs were tested using the Guinea Pig Maximization Test. The intradermal induction used a 12.5% dilution, and the topical induction used undiluted test material. An additional group of 10 animals was used as controls. The animals weighed 304-431 g, and were supplied by Centre de Production Animale (Olivet); the ages of the animals were not reported.

Based on the results of this study, Xedamate-60 *is* a dermal sensitizer.

Since the study indicates the test material is a dermal sensitizer it can be classified as acceptable in satisfying the guideline requirements for a dermal sensitization study (OPPTS 870.2600; OECD 406) in the guinea pig despite some deficiencies in the reporting.

COMPLIANCE: Signed and dated GLP, Quality Assurance and Data Confidentiality statements were provided.

PROCEDURE:

A. Induction: On day 0, each animal received three pairs of intradermal injections. The first pair contained a 12.5% dilution of the test material in physiological saline; the second contained a 50% dilution of Freund's complete adjuvant (FCA) in physiological saline; and the third contained a 1:1 mixture of a 25% dilution of the test material in physiological saline and a 50% dilution of FCA in physiological saline. The study report did not mention the volume of the injections or the location on the body that was used. On day 8, an unspecified volume of the undiluted test material was applied topically to the same site. The application method and duration of exposure were not reported. Reactions to the inductions were not reported.

B. Challenge: Following an 18-day rest phase (on day 27), unspecified volumes of 25% and 12.5% dilutions of the test material in physiological saline were applied topically under an occlusive dressing for 24 hours. The anatomical location was not reported, and the use of a "control" substance was not mentioned. Reactions were scored 48 and 72 hours after application.

C. Rechallenge: Two weeks after the initial challenge, unspecified volumes of 12.5% and 6.25% dilutions of the test material in physiological saline were applied topically under an occlusive dressing for 24 hours. The anatomical location was not reported, and the use of a control substance was not mentioned. Reactions were scored 48 and 72 hours after application.

D. Negative controls: A group of ten animals was designated as negative controls. Although not explicitly stated in the study report, it is assumed that these animals were subjected to induction, challenge and rechallenge in identical manner to the test group, except physiological saline was used during the inductions instead of the test material or dilutions of the test material.

RESULTS and DISCUSSION:

A. Reactions and durations:

1. Treated animals: Following the initial challenge with the 25% dilution, at 24 hours, 4/21, 7/21, and 10/21 sites had erythema scores of 0, 1, and 2, respectively, and at 48 hours, 5/21, 9/21, and 7/21 sites had those same respective scores. Following the initial challenge with the 12.5% dilution, at 24 hours, 7/21, 7/21, and 7/21 sites had erythema scores of 0, 1, and 2, respectively, and at 48 hours, 9/21, 7/21, and 5/21 sites had those same respective scores. Following rechallenge with the 12.5% dilution, at 24 hours, 6/21, 8/21, and 7/21 sites had erythema scores of 0, 1, and 2, respectively, and at 48 hours, 9/21, 5/21, and 7/21 sites had those same respective scores. Following rechallenge with the 6.25% dilution, at 24 hours, 7/21, 7/21, and 7/21 sites had erythema scores of 0, 1, and 2, respectively, and at 48 hours, 11/21, 3/21, and 7/21 sites had those same respective scores. No edema was seen following the initial challenge or the rechallenge.

2. Negative controls: There were no erythema scores greater than 1 at any dilution at either time point following challenge or rechallenge: 3/10 scored 1 for erythema at 24 hours following the first challenge (with 10/10 scoring zero at 48 hours), and 2/10 scored 1 at 24 hours following the second challenge (with 10/10 scoring zero at 48 hours). The same negative control animals were used for both challenge and rechallenge.

B. Positive control: The study report included summarized results from a historical positive control study with neomycin sulfate that was initiated on January 15, 2002. There was no description of the test methods, so it is unknown whether they were identical to those used in the current study.

C. Reviewer's conclusion: In agreement with the study author, the test material is a dermal sensitizer.

D. **<u>Reviewer's note</u>:** The study author did not fully describe the methods used, including the volume and location of the intradermal injections, the volume, location, duration, and application method (use of occlusion, etc.) of the topical induction, the volume and location of the challenge and rechallenge application, any use of a control substance during challenge and rechallenge, and the treatment of the negative controls. The study author also did not provide the grading scale; OECD 406 was cited, but, as erythema and edema were scored separately, the Magnusson and Kligman grading scale provided in OECD 406 was not the one used. The study author cited a study protocol, which presumably included at least some of this information, but a copy of the protocol was not provided. In addition, the test material characterization did not include the percentage(s) of the active ingredient(s).

1. **DP BARCODE:** 354300
2. **PC CODES:** 82070, 018301
3. **CURRENT DATE:** October 27, 2008
4. **TEST MATERIAL:** Clove oils & Chlorpropham; from information received from Lewis & Harrison LLC on 10/20/2008 the material tested contained 58.48 ± 0.77% Chlorpropham and 41.52 ± 0.77% Clove Oil.

Study/Species/Lab Study # / Date	MRID	Results	Tox. Cat.	Core Grade
Acute oral toxicity/rat Phycher Bio développement Study #TAO423-PH-02/0132 / October 3, 2002	47425508	LD_{50} Males > 2000 mg/kg bw LD_{50} Females > 2000 mg/kg bw LD_{50} Combined > 2000 mg/kg bw	III	A
Acute dermal toxicity/rat Phycher Bio développement Study #TAD-PH-02/0132 / October 3, 2002	47425509	LD_{50} Males > 2000 mg/kg bw LD_{50} Females > 2000 mg/kg bw LD_{50} Combined > 2000 mg/kg bw	III	A
Acute inhalation toxicity/rat Safepharm Laboratories Limited Study #1620/041 / November 18, 2002	47425510	LC_{50} Males > 4.67 mg/L LC_{50} Females > 4.67 mg/L LC_{50} Combined > 4.67 mg/L	IV	A
Primary eye irritation/rabbit Phycher Bio développement Study #IO-OCDE-PH-02/0132 / October 3, 2002	47425511	Moderately irritating; MMTS = 42.0 at 24 hours; all eyes were negative for irritation 7 days after exposure to the test material.	III	A
Primary dermal irritation/ rabbit Phycher Bio développement Study #IC-OCDE-PH-02/0132 / October 3, 2002	47425512	Moderate irritant: PII = 2.00	III	A
Dermal sensitization/guinea pig Phycher Bio développement Study #SMK-PH-02/0132 / October 3, 2002	47425513	*Is* a sensitizer	--	A

Core Grade Key: A = Acceptable, S = Supplementary, U = Unacceptable, W = Waived